STATE MEDICAID P&T COMMITTEE MEETING

FRIDAY, November 16, 2007
7:00 a.m. to 8:30 a.m.
Cannon Health Building
Room 114

MINUTES

Committee Members Present:

Lowry Bushnell, M.D.
Thomas Miller, M.D.
Raymond Ward, M.D.
Koby Taylor, Pharm D.
Kort DeLost, R.Ph.
David Harris, M.D.
Duane Parke, R.Ph.
Karen Gunning, Pharm. D.

Board Members Excused:

Jerome Wohleb, Pharm D**.**

Dept. of Health/Div. of Health Care Financing Staff Present:

RaeDell Ashley, R.Ph.
Jennifer Zeleny, CPhT
Tim Morley, R.Ph.
Duane Parke R.Ph.
Lisa Hulbert, R.Ph.

Other Individuals Present:

Bobby White, UCB
Tom Saunders, U of U
Crae Anderson, Alpharma
Alan Bailey, Pfizer
Marianne Paul, U of U DRRC
Sabrina Aery, BMS
Slater Sparks, Sciele Pharma
Chris Kottenstelt, PAC, Alpharma
Alisa Ramailevy, U of U
Linda Tyler, U of U
Kathryn Myers, U of U
Bryan Larson, U of U
Ryan Steed, U of U
Mei-Jen Ho, U of U
Chris Beckwith, U of U

Meeting conducted by: Karen Gunning PharmD., Chairperson.

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1. Business Items: Members of the audience were reminded that information to be considered for the upcoming topics needs to be submitted at least 60 days in advance. Future topics are listed at the bottom of the agenda. Persons wishing to address the P&T Committee need to contact Duane Parke at least 7 days in advance of the meeting.

   For the year 2008, the meetings will still be held on the 3rd Friday of every month, hopefully in Room 125.

   The Department of Health has made decisions regarding Preferred Drugs on the diabetic supplies. The preferred products will be Roche and Lifescan. For the thiazolidinediones, both Actos and Avandia will be on the PDL.

2. Minutes for October 2007 were reviewed and approved.

3. DUR Board Update: Tim Morley addressed the Committee. The DUR Board has reviewed the minutes the proceedings from the past few meetings and has taken leads as to some areas that need to be discussed with the DUR Board. The DUR Board intends to review oral hypoglycemics and the program surrounding opioid analgesics as a result of the P&T Committee's recent discussions.

4. Opiate Analgesics – Long Acting: Chris Beckwith addressed the Committee. The Oregon review process involves selecting a disease state to evaluate and conducting a literature search to come up with key articles that have studied the particular disease state. For this review, Oregon selected adults with chronic non-cancer pain that had lasted at least 6 months. Patients with cancer and HIV were excluded. The medications that they identified as being considered in this review were what they considered long-acting opiates that were given no more than three times per day. The drugs that they included in the class were transdermal fentanyl, oral oxycodone, oral morphone, oral methadone, oral oxymorphone, and oral levorphanol, which are available in the U.S. They also included dihydrocodeine and hydromorphone, which are not currently available in the U.S. Of the drugs considered that are available in the U.S. there are 6 drugs. Transdermal fentanyl, oral oxycodone, oral morphine, and oral oxymorphone are available in controlled-release dosage forms. Methadone and levorphanol have very long half-lives. They evaluated efficacy endpoints of pain intensity, pain relief, and function in their evaluation. They also looked at adverse events of abuse, addiction, nausea, vomiting, constipation, dizziness, somnolence, and confusion. As a surrogate measure of adverse events, they also looked at withdrawal rates and withdrawals due to adverse events. Their preference was to include only randomized controlled trials for efficacy, and for adverse events they included clinical trials and observational studies. From their literature searches, they identified over 1400 articles. From those, they were able to narrow it down to only 25 that were of sufficient quality to make assessments.

   The next thing that Oregon does is to identify key clinical questions to be addressed. For this one, the questions were around efficacy, safety, and use in special populations. Looking at the trials that they identified, only 5 of the 25 directly compared one opiate to another. The trials were very different in size and length of study. The first clinical question that they asked is, "What is the comparative efficacy of these agents for reducing pain and improving function in adults with chronic non-cancer pain?" Overall, they found that there was poor evidence on which to base a therapeutic decision. The question was then broken into three sub-parts. They looked at head-to-head comparisons where one opiate was compared to another. Of those 5 trials, none found any differences in efficacy. The next question looked at trials comparing long-acting opiates to other drugs or placebo to look at an indirect comparison of efficacy. Out of 20 trials that were included, there was actually no useful indirect evidence that allowed them to make a judgment of superiority for any of the long-acting opiates. The next thing they looked at is if long-acting opiates are more effective than short-acting opiates. Again, there was no good-quality evidence to suggest that there was superior efficacy in the long-acting opiates versus short-acting opiates.

   The next question that they asked was the comparative safety of these agents in patients with chronic non-cancer pain. Again, there was a poor level of evidence to draw any therapeutic conclusions. They broke this down similarly. They looked at head-to-head comparisons and found that there was insufficient data to judge that there was any difference between the agents. None of the trials were

specifically designed to address safety, which was one of the limitations. In two trials, withdrawals due to adverse events were more common with transdermal fentanyl. Constipation was more common with the morphine. All of the head-to-head trials excluded patients who were at high risk for abuse or addiction, so it was not clear whether there were differences in abuse potential with these. The second question was whether the long-acting opiates were safer than other medications or safer than placebo. Again, they felt that the data were too heterogeneous and they could not make a determination of that. In general, in retrospective studies, constipation was more common with oral oxycodone than with transdermal fentanyl. Long-acting morphine and transdermal fentanyl in another study were not different in the rate of constipation. Epidemiological data from Oregon found that there was an increase in methadone-associated death that strongly paralleled an increase in methadone prescribing. They felt that this did not suggest that methadone was less safe than other long-acting opioids or that the data were not strong enough to make that decision. The third part of the safety question was whether the long-acting opiates were safer than the short-acting opiates. Again, there were no data to allow them to make a judgment on that. They felt that the evidence was not strong enough to decide.

The last question: "Are there sub-populations of patients, either by race, gender, age, or type of pain for which one long-acting agent was more effective or caused less adverse effects than another?" Again, there is a poor level of evidence and the Oregon reviewers felt that there was not enough information to allow them to make a judgment there. Overall, there was even less information on special populations than there was on the other comparisons.

The University of Utah Drug Information Center also reviewed long-acting Oxymorphone and has prepared a document on that for the P&T Committee. This is a new product in the U.S. and has come out since the Oregon document was prepared. This is a long-acting opiate similar to the others. It has a different release mechanism than the "contins". The key with this drug is that when given with food, peak oxymorphone levels increase by 50%. If taken with ethanol, peak concentrations may increase from 70% to 270%. That is similar to Palladone, which was withdrawn from the market due to toxicity and death. It has been compared in 4 trials with oxycodone extended release and in one trial with morphine extended release. It was at least as effective as the comparator agents, and up to 86% of the patients reported good, very good, or excellent analgesia with oxymorphone as opposed to up to 78% with oxycodone. Adverse events are similar to other agents. Clinical trials for oxymorphone did not make any statistical comparisons with other agents.

Linda Tyler addressed the Committee. The University of Utah Drug Information Center prepared two additional documents for the P&T Committee. The first is Opioid Public Health Concerns. It would be hard for the P&T Committee to consider this without understanding that there is another Opioid Task Force in the State Department of Health. It is trying to address the trend that has been noted over the last several years that Utah, in particular, has a high unintentional death rate due to opioids. This is the case when opioids are used in the usual therapeutic sense. It is often seen in patients who need extended opioid therapy after a hospitalization and it occurs in a short period after they have been started on therapy. The table provided to the P&T Committee shows that the death rates have dramatically increased. Utah has one of the highest rates. A couple of drugs have been particularly associated with that. That would be fentanyl, methadone, and oxycodone. In terms of actual numbers, methadone is probably the highest category. Methadone is special because it has incomplete tolerance with other opioid and dosage tables are misleading with regards to methadone,

because methadone has a very long half-life and takes some time to get to a steady state. Likewise, methadone has QT prolongation. There is a very narrow range to work with for a therapeutic range. This is true of all the opioids, but it is especially true with methadone. As far as patient characteristics that are more often associated with death, it is typically seen in patients who are 45-54 years of age. It is outside of the typical drug seeking population. It was also seen more in rural areas and among women. It was also higher in patients who were overweight or obese. One thing that happens with these patients is that they may have undiagnosed sleep apnea, which creates a higher risk of death. There may be other drugs involved, such as anti-anxiety drugs. Deaths due to alcohol combined with opioids such as methadone have actually decreased in the state. There is a lot of work going on with opioids in the state. The Legislature funded the Opioid Task Force during the last session to use the Controlled Substance Database to start to identify if there are trends or if there are groups of people that need to be educated more. Morphine has not been associated with an increased number of deaths like the other drugs. Suboxone was also not included. Most of these unintentional deaths were outside of the group of patients who abuse drugs.

The last item that the University of Utah Drug Information Center prepared at the request of the P&T Committee was a dosage conversion chart. Conversion charts are one of the things that pain experts would say contribute to not providing optimal therapy. There are many problems with the available conversion charts. There was one place where the dosage conversion charts were published in 1992. That was The Agency for Healthcare Policy Research in collaboration with the Acute Pain Society. While there are many charts in many books, most have this one antecedent source. The problem is that most of the conversions are based on single-dose studies and not repeated-dose studies. This is particularly problematic around methadone, which has a very long half-life and accumulates. Most of the studies were done in opioid naïve patients, rather than opioid tolerant. An opioid tolerant patient would need to be approached differently. Most of the studies were done in acute pain rather than chronic pain studies. All of the conversion failed to take into account incomplete cross-tolerance. This, again, is particularly problematic with regards to methadone. The DRRC believes that most of the dosage conversion charts overestimate the amount of methadone that needs to be used. Looking at the tables taken from the common references that people would be most likely to use, there is a very large variability in doses. In particular, methadone ranges all the way from 2.5mg to 20mg being equivalent. Likewise, there are no similar dose conversions available for fentanyl. Some people say that methadone and fentanyl should only be used by people who are very experienced with managing pain. The Drug Information Center does not recommend that the P&T Committee promote any dosage conversion charts. Each patient needs to be titrated individually when switching opioids.

The Committee had also requested evidence for the concomitant use of long-acting opioids. The Drug Information Center did a Medline search and Cochran Library Search for any information on using more than one of these agents at a time. No evidence was found to support this practice. The only information that was located was clinical practice guidelines from the Department of Veterans Affairs and Department of Defense, which recommended a similar strategy of rotating the opioids. Because of the incomplete cross-tolerance that happens, rotating to a different agent may allow patients to have better pain control with a lower dose of another agent.

The Committee asked if there was any information in the Public Health Concern document about people taking multiple long-acting opioids and if it can contribute to death. The document did look

at concomitant use of anti-depressants. Those were present in some of the ingestions. Alcohol was, as well. However, because of the way that the information came in, there was no way to tell if the patient had taken multiple long-acting opioids.

The Committee asked if there was more addiction liability with short-acting versus long-acting opioids. This was something that the Oregon reviewers attempted to address, but were not able to due to a lack of evidence.

Dr. Ward stated that in his experience patients tend to take higher daily doses of narcotics when taking long-acting versus short-acting medications. Also, pain patients tend to be put on high doses of opioids when referred to a pain clinic. Dr. Beckwith stated that patients taking long-acting opioids are typically also on a short-acting opioid for breakthrough pain, and this was not addressed in the Oregon monograph.

The Oregon studies also included a 40-50 year old age group, and this is not what is typically seen in the primary care setting.

Karen Gunning asked if the Task Force has any opinion about what a Committee like the P&T Committee could do to improve things. The Task Force is not far along enough in their deliberations to have any recommendations for the P&T Committee. Certainly, any action that the P&T Committee would take could complement what the Task Force is attempting to do.

Karen Gunning asked Medicaid to talk about limitations that are already in place for opioid medications. The DUR Board implemented cumulative restrictions in 2004. First off, they restricted that patients cannot get two long-acting opioids concurrently. There is a cumulative limit on the oral tablets of 90 tablets per month on the long-acting opioids. The Fentanyl patches are set at 15 units per 30 days, and the 100mcg patch is only available for cancer pain. For clients with a cancer or end-stage HIV or paget's disease, the ICD.9 code can override the limit on narcotics.

The Committee asked if there has been an increase in the number of prescriptions written in the time when the large increase in the number of deaths. The periods of 1991-1998 and 1999-2003 saw a paradigm shift in how pain was treated, and practitioners were encouraged to treat pain more aggressively. Does the paradigm shift correspond with this change? The data does demonstrate that while the number of prescriptions did increase during this time, the number of deaths increased disproportionately. It is not easy to determine whether or not the doses prescribed per patient were higher because the data was gathered at a macro-level.

Karen Gunning asked if there are any restrictions on methadone. Methadone is restricted to 150 dosage units per month and cannot be used concomitantly with any other long-acting opioids.

Karen Gunning asked if there are many petitions for doses in excess of the usual Medicaid dosage limits. Initially there were, but that seems to have settled down.

Medicaid also covers treatment in a methadone clinic. The methadone in those clinics does not show up in the Pharmacy POS claims or on the Controlled Substance Database.

The Committee asked which long-acting opioids are already available as generics. Morphine, methadone, and fentanyl are available as generics. Oxycontin did have a generic, but it is not consistently available because of the lawsuit against the generic companies.

Chris Kottenstelt of Alpharma addressed the Committee. He represents Kadian. Alpharma provides a strong risk-management program. The first thing that Alpharma did from that standpoint was an in-vivo study of Kadian in combination with alcohol in opioid naïve patients. These patients were blocked with naloxone so that they didn't get the opioid effect. This study demonstrated bioequivalence of the drug and its distribution characteristics in the presence of alcohol. Kadian is available in strengths that allow for incremental dose increases. Alpharma's Navapro system has a monitoring system that monitors the internet looking at certain websites that provide information how to abuse or misuse drugs. Kadian is not out there with mentions, and is mentioned as being disliked by abusers. There is a Task Force with the American Pain Society looking at the use of opioids in non-cancer pain, which should be coming out with guidelines in the next year.

The Committee asked if Suboxone is paid by Medicaid. Medicaid does pay for Suboxone, but there is very little use.

Dr. Ward made a motion that all of the long-acting narcotics are equally efficacious. Duane Parke seconded the motion. The motion was passed unanimously by Lowry Bushnell, M.D., Kort DeLost, R.PhR.Ph., Thomas Miller, M.D., David Harris, M.D., Raymond Ward, M.D., Duane Parke, R.Ph., Koby Taylor, Pharm D., and Karen Gunning, Pharm. D.

Karen Gunning made a motion that oxymorphone not be considered for the PDL due to safety concerns with combining doses with food and alcohol. Dr. Bushnell seconded the motion. The motion was passed unanimously by Lowry Bushnell, M.D., Kort DeLost, R.PhR.Ph., Thomas Miller, M.D., David Harris, M.D., Raymond Ward, M.D., Duane Parke, R.Ph., Koby Taylor, Pharm D., and Karen Gunning, Pharm. D.

Karen Gunning suggested that the DUR Board examine the use of the opioid drugs, particularly methadone, because of the large number of deaths associated with methadone, particularly when prescribed by less experienced clinicians. There is also an access problem for pain clinics, and it is a particularly sever problem for Medicaid patients. Dr. Ward stated that he does not feel that it would be appropriate for the P&T Committee to recommend that Medicaid not use methadone, since it is a cost-effective drug that is very effective when prescribed correctly. However, it would not be appropriate to have methadone as the only preferred agent.

Dr. Ward made the motion that methadone be available as a preferred agent, but not as the only preferred agent. Dr. Taylor asked if all generics would be on the preferred drug list. Fentanyl patches, methadone, and long-acting morphine are all available as generics. Dr. Ward amended his motion to state that among all of the generic agents that are available, the needs of Medicaid patients should be covered. There are no additional branded products that the Committee feels must be included on the PDL. Dr. Miller seconded the motion. The motion was passed unanimously by Lowry Bushnell, M.D., Kort DeLost, R.PhR.Ph., Thomas Miller, M.D., David Harris, M.D., Raymond Ward, M.D., Duane Parke, R.Ph., Koby Taylor, Pharm D., and Karen Gunning, Pharm. D.

The P&T Committee asked if the DUR Board could exclude generics from coverage based on cost. Generally, the DUR Board looks at safety, efficacy, and cost. The Committee was concerned that fentanyl patches remain available, and wanted to make it clear that was the intent of the motion.

Dr. Tyler asked if Medicaid would be picking one preferred drug out of the class. All of the generics will continue to be covered under the PDL. Of the branded products, some may be chosen for the preferred drug list if the secondary rebates are favorable.

The Committee asked if there was a "grandfather" provision for patients who have already been stabilized on a non-preferred narcotic. Medicaid recognizes that this is a larger issue with some drug classes than with others. It would be unwise for Medicaid to require use of a preferred drug in this class. The current private insurance market already requires generics through tiered copays. With the Utah Medicaid PDL, all the physician has to do to keep getting the non-preferred drug is write "Dispense As Written - Medically Necessary" and document the medical necessity in the patient's chart. Medicaid will need to publicize and educate providers about this well in advance. This drug class is not like the PPI's, where patients can transition to the preferred drugs with little notice.

The Committee asked the University of Utah Drug Information Center to provide lists of all of the antihypertensives that are available in each class. Also, the Committee would like to see a list of combination products, and the costs and benefits of the combination products. Karen Gunning requested a review of the drug eplerinone. The Committee would like to have information on the psychiatric side-effects of beta-blockers, particularly Inderal. In terms of fair notice, combination products should probably be put off until February or March, after all of the single-entity drugs have been reviewed by the Committee.

Next Meeting Set for Friday, December 21, 2007.
Meeting Adjourned.

Minutes prepared by Jennifer Zeleny